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2018-12

Fihlman , M , Hemmilä , T , Hagelberg , N M , Backman , J T , Laitila , J , Laine , K , Neuvonen , P J , Olkkola , K T & Saari , T I 2018 , ' Voriconazole greatly increases the exposure to oral buprenorphine ' , European Journal of Clinical Pharmacology , vol. 74 , no. 12 , pp. 1615-1622 . https://doi.org/10.1007/s00228-018-2548-8

http://hdl.handle.net/10138/268045
https://doi.org/10.1007/s00228-018-2548-8

publishedVersion

European Journal of Clinical Pharmacology (2018) 74:1615–1622
https://doi.org/10.1007/s00228-018-2548-8

PHARMACOKINETICS AND DISPOSITION

Voriconazole greatly increases the exposure to oral buprenorphine

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Received: 22 June 2018 / Accepted: 22 August 2018 / Published online: 30 August 2018

Abstract

Purpose Buprenorphine has low oral bioavailability. Regardless of sublingual administration, a notable part of buprenorphine is exposed to extensive first-pass metabolism by the cytochrome P450 (CYP) 3A4. As drug interaction studies with buprenorphine are limited, we wanted to investigate the effect of voriconazole, a strong CYP3A4 inhibitor, on the pharmacokinetics and pharmacodynamics of oral buprenorphine.

Methods Twelve healthy volunteers were given either placebo or voriconazole (orally, 400 mg twice on day 1 and 200 mg twice on days 2–5) for 5 days in a randomized, cross-over study. On day 5, they ingested 0.2 mg (3.6 mg during placebo phase) oral buprenorphine. We measured plasma and urine concentrations of buprenorphine and norbuprenorphine and monitored their pharmacological effects. Pharmacokinetic parameters were normalized for a buprenorphine dose of 1.0 mg.

Results Voriconazole greatly increased the mean area under the plasma concentration–time curve ($AUC_{0–18}$) of buprenorphine (4.3-fold, $P < 0.001$), its peak concentration (C_{max}) (3.9-fold), half-life ($P < 0.05$), and excretion into urine (A_e; $P < 0.001$). Voriconazole also markedly enhanced the C_{max} ($P < 0.001$), $AUC_{0–18}$ ($P < 0.001$), and A_e ($P < 0.05$) of unconjugated norbuprenorphine but decreased its renal clearance ($P < 0.001$). Mild dizziness and nausea occurred during both study phases.

Conclusions Voriconazole greatly increases exposure to oral buprenorphine, mainly by inhibiting intestinal and liver CYP3A4. Effect on some transporters may explain elevated norbuprenorphine concentrations. Although oral buprenorphine is not commonly used, this interaction may become relevant in patients receiving sublingual buprenorphine together with voriconazole or other CYP3A4 or transporter inhibitors.

Keywords Buprenorphine · Norbuprenorphine · Voriconazole · Pharmacokinetics · Drug-drug interaction · CYP3A4 · Transporters

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00228-018-2548-8) contains supplementary material, which is available to authorized users.

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Introduction

Buprenorphine is a partial μ-opioid receptor agonist, which antagonizes κ-opioid receptor and acts as an agonist at the δ-opioid receptor and opioid receptor-like receptor [1, 2]. Buprenorphine is increasingly used for treating acute and chronic pain. Analgesic doses range from 0.3 to 0.6 mg when intravenous or intramuscular dosing routes are used. Buprenorphine is also a good option for substitution therapy to treat opioid dependence because of its pharmacokinetic and pharmacodynamic properties. Buprenorphine produces long-lasting subjective and physiologic effects without significant respiratory depression [3, 4]. Sublingual doses used in opioid substitution therapy are much higher than those used in treatment of chronic pain, but buprenorphine is considered to be safe because of its ceiling effects [4].

Buprenorphine has very low oral bioavailability because of its extensive first-pass metabolism [5, 6]. The bioavailability is higher, about 15–30%, when buprenorphine is administered sublingually [7, 8]. The mean time to maximum plasma concentration following sublingual administration varies from 1 to 3 h [9–12]. After an oral and sublingual buprenorphine administration, extensive first-pass metabolism and large interindividual variability increase the susceptibility to drug interactions. Furthermore, many opioids are substrates to some transporter proteins, such as P-glycoprotein, which can affect their absorption and systemic clearance [13–15].

The main metabolic pathway (65%) of buprenorphine is cytochrome P450 (CYP) 3A4/5-mediated N-dealkylation of the drug, which yields an active metabolite, norbuprenorphine. CYP2C8 and CYP2C9 have been also shown to metabolize buprenorphine [16–19]. Buprenorphine and norbuprenorphine are conjugated to their 3-glucuronides mainly by the UDP-glucuronosyl transferases (UGT) 2B7 and 1A1, and 1A3 and 1A1, respectively [5, 20, 21]. Previous study with 63Ni electron-capture gas chromatographic assay evaluated the levels buprenorphine and its metabolites in human urine and feces [22], and approximately 10–30% of the dose was excreted in urine, mainly as conjugated metabolites. Similar results have been published, showing that 15% of conjugated metabolites are excreted in urine [5], and only small amounts of unconjugated parent drug or norbuprenorphine are excreted into urine; most of the dose is eliminated in the feces [5, 23].

The effect of strong CYP3A4 inhibitors on the pharmacokinetics of buprenorphine is largely unknown, particularly after its oral ingestion. A previous study showed that ketoconazole does not have clinically significant interactions with transdermally delivered buprenorphine [24]. Other interaction studies have been conducted with patients receiving simultaneous buprenorphine substitution and antiretroviral therapy [25]. Voriconazole is frequently used in immunosuppressed patients with suspected aspergillosis. Voriconazole is a potent inhibitor of CYP3A4, CYP2B6, CYP2C9, and CYP2C19 enzymes [26–28]. Oral buprenorphine is not commonly used in clinical settings, but very large doses of sublingual buprenorphine from 16 to 32 mg are administered in substitution therapy [29, 30]. A considerable part of the sublingual dose can be swallowed, making buprenorphine susceptible to first-pass metabolism in the gut wall and liver [7, 31]. Here, we wanted to study the pharmacokinetics of oral buprenorphine after its immediate swallowing, with or without voriconazole, to evaluate the magnitude of interaction after their possible concomitant ingestion.

Materials and methods

Study participants

In view of our previous studies [12, 32], it was calculated that ten subjects would be needed to detect a 30% difference in the area under the plasma concentration–time curve ($AUC_{0-\infty}$) of buprenorphine at a power of 80% and level of significance of $P < 0.05$. To also consider potential dropouts, we recruited 12 healthy non-smoking volunteers (4 females and 8 men; age range 18 to 29 years; body mass index from 20.5 to 27.8 kg/m^2). E-mail announcements, assigned to university students, were used to recruit participants. A written informed consent was obtained. The criteria for exclusion included concomitant drug therapy, previous history of intolerance to any of the drugs studied, past history of significant disease, alcoholism, drug abuse or psychological or emotional problems, blood donation within 4 weeks prior to study, and participation in any other studies involving drug products within 1 month prior to this study. Female participants were given instructions to use safe non-hormonal contraception during the study because hormonal contraceptives were not allowed. Clinical examination and routine laboratory tests were performed to evaluate participants' physical health. Their medical history was also evaluated, and all 12 participants were found to be in good physical health. Urine toxicology and pregnancy tests were negative and ECGs were in normal limits. The Finnish translation of the Abuse Questions [33] was used to evaluate the risk of participants to develop opioid abuse, and the risk was found to be low for every participant. Volunteers were not allowed to consume coffee, tea, and energy drinks or grapefruit juice during the study.

Study outline and drug administration

The study protocol was approved by the ethics committee of the Hospital District of Southwest Finland and by the Finnish National Agency for Medicines and was registered in the EudraCT clinical trials register under code 2011-001939-23. The clinical phase of the study was conducted in the research facilities of the Department of Clinical Pharmacology and TYKSLab, University of Turku and Turku University Hospital, Finland. The volunteers ingested orally, in randomized order either voriconazole or placebo for 5 days. Dosing of voriconazole (Vfend® 200 mg tablet; Pfizer, Sandwich, Great Britain) was 400 mg at 8.00 and 20.00 on day 1, 200 mg at 8.00 and 20.00 on days 2–4, and 200 mg at 10.00 and 20.00 on day 5. The washout interval in this cross-over study was 4 weeks. On the fifth day of pretreatment, all subjects ingested a single dose of 0.2 mg (3.6 mg during placebo phase) of oral buprenorphine (Temgesic® 0.2 tablet RB Pharmaceuticals Limited, Slough, Great Britain) with 200 ml of water at 11.00 on empty stomach.

Adherence with the voriconazole/placebo dosing schedule was assessed using mobile phone text messages. After taking each dose, the subjects sent a mobile phone text message to one of the investigators. The investigator contacted the subject if no text message was received within 15–20 min after scheduled dosing time and reminded them to take the dose. The volunteers fasted overnight (8 h) before the administration of buprenorphine. Standardized meals were served 4 and 8 h after buprenorphine ingestion.

Blood sampling and drug analysis

On the test days, a forearm vein was cannulated, and timed blood samples (10 ml) for pharmacokinetic measurements were collected into ethylenediaminetetraacetic acid-containing tubes immediately before and 0.5, 1, 1.5, 2, 3, 4, 5, 6, 8, 10, 12, and 18 h after the ingestion of buprenorphine. Plasma was separated within 30 min and stored at − 70 °C until drug analysis. Urine was collected up to 18 h after buprenorphine administration. Urine aliquots were stored at − 70 °C until analysis.

The concentrations of buprenorphine and norbuprenorphine in plasma and urine samples were analyzed with a validated liquid chromatography tandem mass spectrometric method as previously described [12]. The low limit of quantification (LLQ) for plasma and urine buprenorphine was 0.02 ng/ml and for norbuprenorphine 0.05 ng/ml. Concentrations below the LLQ but clearly detectable were used as LLQ/2 in calculation of the mean (SD) concentrations. The interday coefficients of variation (CV%) were for buprenorphine 8.0% at 5.3 ng/ml, 8.7% at 0.53 ng/ml, and 6.1% at 0.053 ng/ml and for norbuprenorphine 3.7% at 4.8 ng/ml, 8.7% at 0.48 ng/ml, and 11.9% at 0.048 ng/ml.

Plasma concentrations of voriconazole were determined from the samples taken on day 5 before administration of buprenorphine by using liquid chromatograph equipped with Waters Symmetry C8 column (Waters) and UV detection at 255 nm wave length as described before [34]. Diazepam was used as the internal standard. The LLQ for voriconazole was 10 ng/ml. The CVs for voriconazole were below 10% at relevant plasma concentration range, i.e., 7.5% at 4000 ng/ml, 3.0% at 1100 ng/ml, and 5.5% at 110 ng/ml.

Pharmacokinetic measurements

The peak plasma concentrations (C_{max}) and corresponding time to C_{max} (t_{max}) of buprenorphine and norbuprenorphine were observed directly from the data. The areas under the buprenorphine and norbuprenorphine plasma concentration–time curves (AUC) from 0 to 18 h ($AUC_{0–18}$) were calculated by non-compartmental methods using WinNonlin pharmacokinetics program (version 4.1; Pharsight, Mountain View, CA). The terminal log-linear part of each concentration–time curve was identified visually, and the elimination rate constant (k_e) was calculated from the logarithmically transformed data using linear regression analysis. The $t_{1/2}$ was calculated using the equation $t_{1/2} = \ln 2/k_e$. The cumulative amount of unconjugated buprenorphine and unconjugated norbuprenorphine excreted into urine was calculated from 0 to 18 h (A_e), and the renal clearance (Cl_{renal}) using the equation $= A_e/AUC_{0–18}$. All pharmacokinetic parameters were normalized for a buprenorphine dose of 1.0 mg.

Statistical analysis

The $AUC_{0–18}$ of buprenorphine was the primary outcome variable in the study, and all other pharmacokinetic and all pharmacodynamic parameters were secondary variables. Geometric mean ratios with 90% CIs were calculated for the pharmacokinetic variables. Lack of interaction was assumed if the 90% CI of the geometric mean ratios for pharmacokinetic variables were within the acceptance limit of 0.8–1.25. Pharmacokinetic variables and pharmacological effects were compared with paired Student's t test. The values for t_{max} were compared by the use of Wilcoxon signed rank test. The statistical significance level was $P < 0.05$. The Pearson product moment correlation coefficient was used to investigate the possible relationship between the ratios of the $AUC_{0–18}$ of buprenorphine during the treatment phase (voriconazole) to the $AUC_{0–18}$ of buprenorphine during the control phase, as well as to the C_{trough} of voriconazole before the administration of buprenorphine. The associations of plasma buprenorphine concentrations with psychomotor and analgesic effects were also calculated using the Pearson's product moment correlation coefficient. The results are expressed as mean values and variation in data set is expressed as standard deviation (SD). R software (version 3.2.0) and ggplot2 (version 2.1.0) were applied for statistical analysis and graphical presentation.

Results

Voriconazole affected strongly on the pharmacokinetics of orally administered buprenorphine and increased its effects (Fig. 1; Supplementary Figs. 1 and 2; Table 1; Supplementary Tables 1 and 2).

Buprenorphine

Compared to placebo phase, voriconazole increased the mean $AUC_{0–18}$ of oral buprenorphine 4.3-fold (90% CI 2.7, 6.7 $P < 0.001$) and its C_{max} 3.9-fold (90% CI 2.6, 5.9; $P < 0.001$) (Table 1; Supplementary Fig. 2). Voriconazole had no significant effect on the t_{max}, but it slightly prolonged the $t_{1/2}$ of buprenorphine ($P = 0.042$). Voriconazole increased the amount of unconjugated buprenorphine excreted in urine

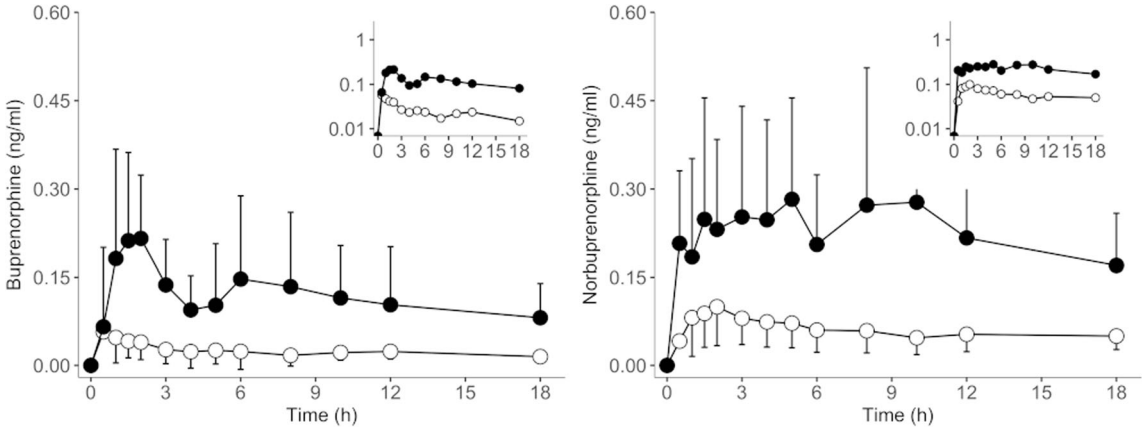

Fig. 1 Mean (SD) plasma concentrations of buprenorphine and norbuprenorphine in 12 healthy subjects after 3.6 mg (placebo phase) or 0.2 mg (voriconazole phase) of oral buprenorphine on the fifth day of pretreatment with placebo (empty circle) or voriconazole (filled circle) 400 mg twice on day 1 and 200 mg twice on days 2–5. Concentrations are shown both on an arithmetic and a semilogarithmic scale (inset). Values are normalized for an oral dose of 1.0 mg

($P < 0.001$; Supplementary Fig. 1) but had no significant effect on its Cl_{renal}. The A_e of unchanged (unconjugated) buprenorphine was less than 0.1% of the dose during 18 h even during the voriconazole phase.

Norbuprenorphine

Voriconazole increased the mean $AUC_{0–18}$ of norbuprenorphine nearly 4-fold (90% CI 3.0, 5.3; $P < 0.001$) and its C_{max} 3.3-fold (90% CI 2.4, 4.4; $P < 0.001$) compared to placebo phase (Table 1). The metabolite to the parent drug ratio (AUC_m/AUC_p) was not changed by voriconazole. Voriconazole enhanced the A_e of unconjugated norbuprenorphine by only 1.5-fold ($P = 0.029$), and accordingly, voriconazole significantly ($P < 0.001$) reduced its Cl_{renal} (Supplementary Fig. 2).

Voriconazole

The mean (SD) plasma concentration of voriconazole (C_{trough}) was 1022 (1509) ng/ml before the administration of buprenorphine during the voriconazole phase, and the concentrations ranged from 170 to 5715 ng/ml.

Table 1 Pharmacokinetic parameters of buprenorphine and norbuprenorphine after oral administration of 3.6 mg (placebo phase) or 0.2 mg (voriconazole phase) buprenorphine on the fifth day of pretreatment with voriconazole (400 mg twice on day 1, 200 mg twice on days 2–5) or placebo in 12 healthy subjects

Parameter	Placebo	Voriconazole	*P* value	Geometric mean ratio (90% CI)
Buprenorphine				
C_{max} (ng/ml)	0.057 ± 0.031	0.22 ± 0.23	< 0.001	3.87 (2.55, 5.88)
t_{max} (h)	0.5 (0.5–18)	2 (0.5–10)	0.06	–
$AUC_{0–18}$ (ng h/ml)	0.43 ± 0.26	2.1 ± 1.4	< 0.001	4.27 (2.71, 6.73)
$t_{1/2}$ (h)	9.1 ± 2.4	14.5 ± 6.8	0.042	1.43 (1.08, 1.89)
A_e (μg)	0.10 ± 0.063	0.53 ± 0.29	< 0.001	6.76 (4.68, 8.83)
CL_{renal} (l/h)	0.31 ± 0.23	0.73 ± 1.3	0.206	0.51 (0.053, 4.89)
Norbuprenorphine				
C_{max} (ng/ml)	0.11 ± 0.025	0.28 ± 0.26	< 0.001	3.29 (2.44, 4.43)
t_{max} (h)	2 (0.5–12)	5 (0.5–8)	0.35	–
$AUC_{0–18}$ (ng h/ml)	1.07 ± 0.58	4.0 ± 2.1	< 0.001	3.95 (2.97, 5.26)
$t_{1/2}$ (h)	13.1 ± 9.06	17.8 ± 7.9	0.12	1.52 (0.98, 2.38)
AUC_m/AUC_p	3.0 ± 1.5	3.8 ± 5.8	0.78	0.92 (0.57, 1.51)
A_e (μg)	6.9 ± 3.3	11.6 ± 7.8	0.029	1.54 (1.20, 1.98)
CL_{renal} (L/h)	7.2 ± 2.7	2.9 ± 1.2	< 0.001	0.39 (0.29, 0.52)

Values are normalized for an oral dose of 1.0 mg. Data are shown as mean ± standard deviation (SD) and as the geometric mean ratios with the 90% confidence interval (CI) in parenthesis—except for t_{max}, which is given as median and range

CI confidence interval, C_{max} peak plasma concentration, t_{max} concentration peak time, $AUC_{0–18}$ area under curve from 0 to 18 h, $t_{1/2}$ elimination half-life, A_e amount excreted into urine within 18 h, CL_{renal} renal clearance

Pharmacological effects and adverse effects

Buprenorphine caused moderate pharmacological effects (Supplementary Table 1), but their relevant comparison between the study phases is not possible due to different buprenorphine doses. The most common adverse effects were mild dizziness and nausea (Supplementary Table 2). There were no severe adverse effects, and tropisetron, naloxone, or any other rescue medication was not needed.

Discussion

We investigated the effect of voriconazole on buprenorphine pharmacokinetics when buprenorphine was swallowed immediately after its oral administration. Although oral ingestion is not commonly used in clinical practice with buprenorphine, a considerable part of the sublingual buprenorphine dose is usually swallowed and therefore susceptible to first-pass metabolism. Furthermore, in some deliberate overdoses, subjects can swallow buprenorphine concomitantly with other drugs, which could inhibit buprenorphine metabolism and increase respiratory depression. Our major finding was that voriconazole greatly increases the exposure to both parent buprenorphine and its active metabolite, norbuprenorphine, in some subjects even 6-fold. On average, voriconazole increased the AUC of oral buprenorphine two to three times more than what we observed in a previous study using sublingual administration [12].

There are only few previous studies characterizing the interactions between buprenorphine and drugs which affect its pharmacokinetics. Most of these studies have focused on high-dose sublingual buprenorphine substitution therapy. Atazanavir alone and with ritonavir increased the AUC of buprenorphine and norbuprenorphine nearly 2-fold and lead to an increased sedative effect [25]. Darunavir–ritonavir or fosamprenavir–ritonavir combinations did not cause significant changes in plasma buprenorphine or norbuprenorphine levels [35]. Boceprevir increased plasma buprenorphine concentrations slightly but decreased norbuprenorphine concentration in plasma [36]. Similarly, lopinavir–ritonavir did not affect buprenorphine pharmacokinetics but did increase the clearance of norbuprenorphine [37]. We showed, recently, that voriconazole and posaconazole increase exposure to sublingual buprenorphine [12]. Rifampicin decreased the exposure to sublingual but not to intravenous buprenorphine [32]. These results seem to emphasize the significant role of CYP3A-mediated first-pass metabolism of buprenorphine, which sublingual administration only partially bypasses.

The metabolic fate of buprenorphine is complicated, and all its details are still not fully elucidated. Buprenorphine is extensively N-dealkylated to norbuprenorphine, mainly by CYP3A4 [16, 17] and to some extent by CYP2C8 [18]. Also, minor CYP3A4- and CYP2C8-catalyzed buprenorphine hydroxylation pathways have been identified [18, 19, 38]. Voriconazole is a potent (K_i values << 10 μM) reversible inhibitor of CYP2B6, CYP2C9, CYP2C19, and CYP3A enzymes [28]. The K_i of voriconazole as a reversible inhibitor of the CYP3A4-dependent formation of norbuprenorphine has been estimated to be 5.91 μM [38]. In the present study, the average plasma trough concentrations of voriconazole were around 3 μM, which suggests a marked inhibition potential for CYP3A4 during the whole 12-h dosing interval. The effects of voriconazole on parent buprenorphine can be mainly explained by inhibition of CYP3A4 during the first-pass and elimination phases. However, the substantial increases in the AUC and C_{max} of norbuprenorphine suggest the presence of additional mechanisms because inhibition of CYP3A4 should decrease the N-dealkylation of buprenorphine to norbuprenorphine.

Buprenorphine and norbuprenorphine are also glucuronidated. UGT2B7 accounts for more than 40% of buprenorphine glucuronidation, while norbuprenorphine glucuronidation is predominantly mediated by UGT1A3 [21]. Buprenorphine and norbuprenorphine are excreted in bile as their glucuronides, but hydrolysis to unconjugated forms by colonic bacterial beta-glucuronidases allows their reabsorption and enterohepatic circulation. Feces contain buprenorphine and norbuprenorphine predominantly in unconjugated form; in urine, they are mainly in conjugated form [5]. Effects of voriconazole and its metabolites on different UGTs and glucuronidases are not known. However, according to a semiphysiological population pharmacokinetic model, voriconazole emerges as an UGT2B inhibitor in the gut and liver [39].

Voriconazole reduced the Cl_{renal} of norbuprenorphine but not that of buprenorphine. Previously, voriconazole has been shown to decrease the Cl_{renal} of diclofenac [40]. Reduction of Cl_{renal} values can be explained by inhibition of membrane transporters as norbuprenorphine, but not buprenorphine, is a substrate of the efflux transporter P-glycoprotein [20]. Because the urinary excretion of (unconjugated) norbuprenorphine was very small, reduction of its Cl_{renal} cannot alone explain its high plasma concentrations. However, voriconazole (or its metabolites) may have affected transporters also in extrarenal tissues, and these effects may have influenced the tissue distribution of norbuprenorphine. P-glycoprotein is a major determinant of norbuprenorphine brain exposure [20], whereas buprenorphine as a lipophilic compound rapidly penetrates cell membranes without transporters. P-glycoprotein can be found in the intestinal wall, blood–brain barrier and many other tissues [41]. Thus, inhibition of P-glycoprotein and/or other transporters could influence, e.g., enterohepatic circulation and tissue concentrations of norbuprenorphine. Of note, norbuprenorphine does not have a ceiling effect on respiratory depression, and respiratory

toxicity of buprenorphine can result from the blockade of P-glycoprotein-mediated efflux of norbuprenorphine at the blood–brain barrier [42]. Further studies are needed on the effect of drug interactions on norbuprenorphine tissue distribution and buprenorphine toxicity, keeping in mind also "opioid toxicity epidemic" [43].

In the present study, relevant comparison of pharmacological effects between the two phases was not possible because of different buprenorphine doses. We used only relatively small doses to minimize the risk of adverse events in healthy volunteers. The dose during the placebo phase (3.6 mg vs. 0.2 mg) was set higher, because we assumed a low oral bioavailability after immediate ingestion of the tablet. On the contrary, we wanted to keep the dose in the voriconazole phase smaller, because of the possibility of strong inhibition of buprenorphine metabolism. We based this assumption on the previous results which have established that voriconazole, and other CYP3A4 inhibitors can dramatically increase exposure to drugs that are metabolized via CYP3A4 [44–51]. We assumed dose linearity since recent reports have demonstrated that buprenorphine shows a linear increase in the exposure across a wide dose range from 0.060 to 12 mg [52, 53].

We acknowledge that our study has limitations which include that it was designed mainly to evaluate the pharmacokinetics of buprenorphine. For this goal, we normalized the pharmacokinetic values to an oral buprenorphine dose of 1 mg. This made doze normalization challenging in pharmacodynamical calculations and in estimating subjective adverse effects. However, dose normalization cannot be used for pharmacodynamical results and subjective adverse effects. We drew blood samples for 18 h, and longer sampling time might have increased the reliability in the pharmacokinetic calculations, especially in determining the elimination half-life. Therefore, the values of elimination half-life and renal clearance should be interpreted with these limitations in mind. The strengths of our study were the two-phase cross-over design and the controlled conditions that confirmed the compliance to blood sampling and urine collection. Using current study design, we could also avoid a possible pharmacokinetic interference caused by naloxone on the interaction between buprenorphine and voriconazole.

In conclusion, our results show that clinically used doses of voriconazole greatly increase the exposure to oral buprenorphine. Although oral buprenorphine is not commonly used in clinical settings, strong inhibition of its first-pass metabolism should be taken into account also when voriconazole or other potent CYP3A4 inhibitors are prescribed to patients receiving sublingual buprenorphine. Patients should be well informed and familiarized with sublingual dosing, as some part of the dose is easily ingested and swallowed. Further studies are warranted on the effect of transporter inhibitors on norbuprenorphine pharmacokinetics and pharmacodynamics because its high concentrations could increase buprenorphine toxicity.

Acknowledgements We thank Mrs. Elina Kahra (medical laboratory technologist, Clinical Pharmacology, TYKSLAB, Hospital District of Southwest Finland, Turku, Finland) for her skillful technical assistance.

Authors' contributions Mari Fihlman took care of the clinical phase of the study and data collection, participated in data analysis and statistical analysis, and wrote the manuscript. Klaus Olkkola and Kari Laine designed the study, wrote the protocol, supervised and coordinated the clinical implementation of the study, and participated in data analysis and manuscript preparation. Tuija Hemmilä participated the clinical phase and data collection. Janne T. Backman, Jouko Laitila, and Pertti J Neuvonen performed the analytical assays and participated in manuscript preparation. Teijo Saari analyzed the data, performed statistical analysis, and wrote the manuscript. All authors materially participated in the research and/or manuscript preparation. All authors have contributed to and approved the final manuscript.

Funding information

This study was supported financially by Turku University Hospital research fund (EVO 13821), Turku, Finland.

Compliance with ethical standards

The study protocol was approved by the ethics committee of the Hospital District of Southwest Finland and by the Finnish National Agency for Medicines and was registered in the EudraCT clinical trials register under code 2011-001939-23.

Conflict of interest The authors declare that they have no conflict of interest.

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